Brain perfusion SPECT analysis

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Chapter 2. FDG-PET for Prediction of AD Dementia in Mild Cognitive Impairment. A Review of the State of the Art with Particular Emphasis on the Comparison with Other Neuroimaging Modalities (MRI and Perfusion SPECT)

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As published in Current Alzheimer Research. 2017; 14(2): 127-142

ABSTRACT

This review article aims at providing a state-of-the-art review of the role of fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging (FDG-PET) in the prediction of Alzheimer's dementia in subjects suffering mild cognitive impairment (MCI), with a particular focus on the predictive power of FDG-PET compared to structural magnetic resonance imaging (sMRI). We also address perfusion single photon emission computed tomography (SPECT) as a less costly and more accessible alternative to FDG-PET.

A search in PubMed was performed, taking into consideration relevant scientific articles published in English within the last five years and limited to human studies. This recent literature confirms the effectiveness of FDG-PET and sMRI for prediction of AD dementia in MCI. However, there are discordant results regarding which image modality is superior. This could be explained by the high variability of metrics used to evaluate both imaging modalities and/or by sampling/population issues such as age, disease severity and conversion time. FDG-PET seems to outperform sMRI in rapidly converting early-onset MCI individuals, whereas sMRI may outperform FDG-PET in late-onset MCI subjects, in which case FDG-PET might only provide a complementary role. Although FDG-PET performs better than perfusion SPECT, current evidence confirms perfusion SPECT as a valid alternative when FDG- PET is not available. Finally, possible future directions in the field are discussed.

1. INTRODUCTION

In 2010, based on evidence accumulated over decades, a hypothetical model was proposed that established a relationship between the stages through which Alzheimer's disease (AD) evolves and the presence of two distinct types of biomarkers [1]. The first imaging biomarker type reflects the cerebral amyloid burden as initial event of AD (amyloidosis biomarker) and presumably presents many years before the first clinical symptoms appear. In autosomal dominant AD for example, Aβ depositions have been reported to be present in the brain 15 years prior to the onset of symptoms [2]. The second biomarker of neuronal injury reflects functional and structural changes that occur later in the successive stages of AD, which include the transition stage of mild cognitive impairment (MCI) and, finally, dementia. In recent years, new data have corroborated this biomarker model [3-6], but have also led to speculations that amyloidosis and neurodegeneration may take parallel paths and not necessarily sequential ones [6-8].

In 2011 the National Institute of Aging-Alzheimer's Association (NIA-AA) provided revised diagnostic criteria for AD [9], which for the first time recognized the use of biomarkers as an adjunct to increase the diagnostic confidence of dementia due to AD, although mainly intended for clinical research purposes. Two biomarkers were recommended for determining the presence of cerebral amyloidosis: one based on measurements of soluble β amyloid (Aβ) 42 in the cerebrospinal fluid (CSF) [10, 11] and the second based on positron emission tomography (PET) amyloid imaging [12]. Likewise, three biomarkers of neuronal injury were recommended: one based on measuring CSF tau protein (CSF tau) [10, 11], another one on 18F-fluorodeoxyglucose (FDG) PET imaging (FDG-PET) [13], and the last one based on hippocampal atrophy measured with structural magnetic resonance imaging (sMRI) [14]. The NIA-AA criteria of MCI due to AD (or the

prodromal AD stage) additionally included perfusion single photon emission computed tomography (SPECT) as a biomarker of neuronal injury, similar to FDG-PET [15].

The prodromal stage of AD (MCI due to AD) is becoming increasingly important in clinical and research settings. Besides clinical criteria of MCI due to AD, the combined presence of both a positive biomarker of cerebral amyloidosis and neuronal injury has a role in maximizing the likelihood that a MCI patient over time converts to AD dementia [15]. With regard to the disease progression in the MCI stage, neuronal injury biomarkers seem to have a more significant role than amyloid biomarkers. The former are more associated with oncoming cognitive deterioration than the latter, which are elevated already in the initial asymptomatic stage of AD, and are close to a plateau at the MCI phase with few further changes [1, 3]. This means that a positive amyloid status by itself reveals little predictive information concerning progression of the disease in the MCI stage. Thus, neuronal injury biomarkers have added value when used as entry criteria or as outcome measures in clinical trials for the evaluation of potential disease- modifying therapies in MCI patients. Other probable modifiers of disease progression include APOE genotype, cognitive reserve (related to educational level), and co-morbidity of other cerebral diseases or lifestyles [6].

In the last decade, FDG-PET has been investigated extensively as an adjunct to predict AD dementia in MCI individuals [15- 24], as well as the subject of several recent reviews [26-32], and of a recent editorial on this topic on behalf of the European Association of Nuclear Medicine [33].

One of the main focuses of the comparative literature in the last five years has been the comparison of FDG-PET with structural imaging modalities, especially sMRI [34-48]. In 2009, Yuan et al. [26] published a meta-analysis showing that FDG-PET outperforms sMRI. Recent studies support this conclusion [34-38]. However, other studies point to

sMRI as being a superior method [39-42] or suggest that the combination of these imaging modalities may either be redundant or complementary [46-48]. Also papers have appeared that aimed at understanding these discrepancies [43, 45]. It has been suggested that sMRI is probably more related to the current cognitive state at the MCI phase, perhaps reflecting permanent damage, whereas FDG-PET might be a more sensitive biomarker of disease progression, and thus might have more predictive value. Although the use of FDGPET as neuronal injury imaging biomarker in AD and other neurodegenerative diseases is gaining approval, there is a need for periodic reviews on this central question to identify new clinical perspectives and research directions. The aim of this article is to present a state-of-the-art review on FDGPET for predicting conversion to AD in MCI patients, focusing on these studies that compare the performance of FDG-PET and sMRI for single-subject prediction. We also address perfusion SPECT as a less costly and more accessible alternative to FDG-PET. For this purpose, a search in PubMed was performed, taking into consideration relevant scientific articles within the last five years, limited to human studies and published in English. Possible future directions are also discussed.

2. FDG-PET FOR PREDICTING AD DEMENTIA IN MCI

2.1. AD-like Pattern by FDG-PET

FDG-PET is an indicator of regional brain glucose metabolism, which in turn is closely related to cell cytoarchitecture and synaptic function [49]. Thus, in case of neurodegenerative diseases such as AD, FDG-PET may be useful to detect neuronal injury or synapse dysfunction associated with the disease.

According to recent guidelines, FDG-PET may be used to increase diagnostic confidence in ‘probable AD’ and to identify cases of ‘possible AD’ in subjects with symptoms atypical of AD [9]. The typical AD- like hypometabolic pattern consists of a regional decrease of FDG uptake in temporoparietal cortices [50, 51]. This pattern, or its variants, may be used

to predict conversion from MCI to AD dementia, and to differentiate AD dementia from other dementia types at an early stage. However, since there is a direct association between regional brain hypometabolism detected by FDG-PET and cognitive impairment severity [34], the AD-like pattern may be less pronounced in MCI due to AD and early AD dementia. Indeed, as shown below (Fig. 1), MCI is a clinical condition which may be prodromal to AD but also to a variety of other dementia syndromes. Although visual reading of FDG-PET scans is irreplaceable for different reasons [50], in borderline situations addition of a quantitative validated metric has been shown to improve accuracy for detection of the AD-like pattern [53, 54]. There have been important advances in metrics for detecting the AD-like pattern [35, 55-64]. This is illustrated by (Fig. 1), showing examples using single-case statistical parametric mapping (sc-SPM) metric in different MCI subjects [58]. The sc-SPM method is considered an excellent metric to detect the AD-like pattern in MCI [45].

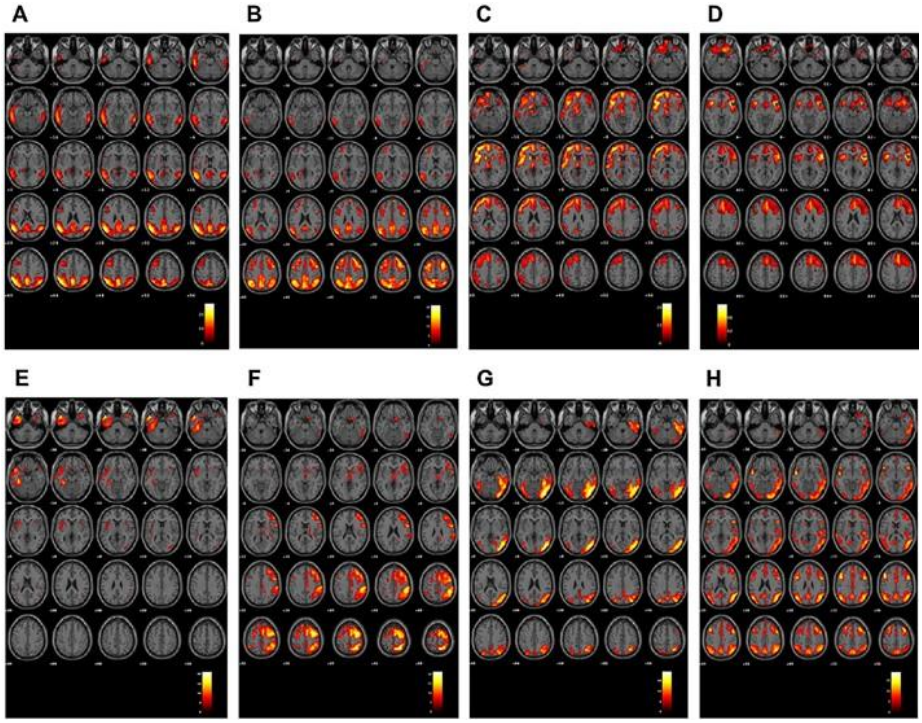

Fig. (1). The SPM-t maps of hypometabolism of eight MCI cases, as example: PET patterns corresponding to Alzheimer's disease (A, B), behavioral variant of frontotemporal dementia (C, D), semantic variant of primary progressive aphasia (E), corticobasal degeneration (F), dementia with Lewy bodies (G, H). Yellow/red scales shown in SPM maps are regions which are hypometabolic in MCI patients in comparison to the normal control database. From C. Cerami et al. NeuroImage: Clinical 7:187-194 (2015).

2.2. AD-Related Atrophy by Structural MRI

Volumetric high-resolution T1-weighted MRI, by 1.5 T or 3 T scanners, is the standard for structural brain imaging (abbreviated above as sMRI). This technique provides images of very high quality in terms of spatial resolution (≈1mm) and tissue contrast, and thus is suitable to measure global and regional brain atrophy in AD. Brain atrophy, especially in medial temporal regions, correlates well with both episodic memory impairment [65, 66]

and tau deposition [67, 68]. Therefore, it is a relevant neuronal injury biomarker of the disease process, including the MCI stage (Fig.2).

Besides visual reading of sMRI, various metrics are available to quantify atrophy, using it as a predictor of AD dementia in MCI subjects. The most commonly applied metrics include: 1) manual segmentation of medial temporal regions, particularly the hippocampus; 2) semi- [69,70] and fully automated [37] methods to measure hippocampal volume; 3) a software package developed by the University of California, San Diego (UCSD) that comprised various volumetric MRI measurements [71], including the hippocampus, the entorhinal cortex, lateral/inferior temporal cortices, the whole brain and ventricles; 4) voxel-based morphometry (VBM), which allows examining differences of regional differences in grey matter volume (for the whole brain) between patients and a normal database, using the SPM approach (Fig. 2C) [72]; 5) deformation-based morphometry (DBM), which uses deformation fields to register brain images to a template [73]. The most popular variant of DBM is tensor based morphometry, which is especially useful for longitudinal studies [74]; 6) surface-based morphometry (SBM) which allows reconstruction of the surface of the boundary between different tissue classes [75]. Freesurfer software is one of the most widespread toolboxes to estimate volume and cortical thickness using SBM methodology [76]; and 7) independent component analysis (ICA) to extract non redundant sources of information from whole-brain data [38].

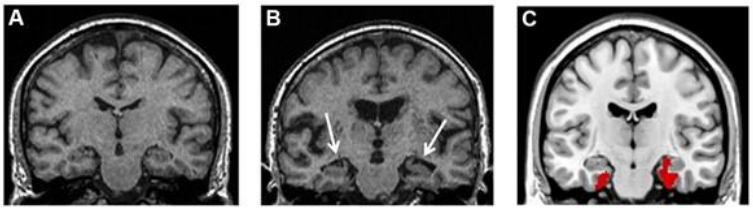

Fig. (2). Coronal T1-weighted MRI corresponding to a normal subject (A) and an amnestic MCI patient (B). Visual inspection of Figure 2.B clearly shows hippocampal atrophy (indicated by white arrows) and ventricular dilatation in the MCI patient, which are both markers of progression to AD dementia over time. Fig. (2C) shows results of voxel-based morphometry (SPM-t map in red) of the MCI patient. This metric quantitatively estimates the degree of grey matter volume reduction of the patient compared with a normal database. As can be observed, the MCI patient showed reduced gray matter volume in the hippocampus and entorhinal cortex. Both subjects were examined in the Center for Neurological Restoration, Havana, Cuba.

2.3. FDG-PET *versus* Structural MRI

In the last five years several studies have been performed which suggest FDG-PET has superior prognostic value over sMRI in individuals with MCI [34-38]. Other studies have reported the opposite [39-42]. The majority of these studies have been conducted using information from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset (controls, MCI and AD patients). ADNI is a multicenter project, which started in North America and provided a platform for the identification and assessment of AD biomarkers [77]. There have also been studies using other datasets [36, 37]. In their analysis of biomarkers (predictors), most studies performed tests for each predictor individually (univariate analysis) and jointly (multivariate analysis). Table 1 summarizes relevant data of the studies that compared FDG- PET and sMRI, individually and in combination with other predictors. These studies are discussed below.

Table 1. Relevant studies in the last five years that compared the performance of FDG-PET and sMRI for predicting conversion in mild cognitive impairment, individually and in combination with other predictors.

Study	Participants	Age (years)	MMSE	Follow up (months)	Best predictor individually	Best combination of predictors
Landau et al. (2010)	Converters= 28 Non converters= 57	78.3 ± 7.5 78.0 ± 7.4	26.4 ± 1.7 27.3 ± 1.6	22.8 ± 4.8	**FDG-PET**; Metric: metaROI [52] HR= 2.94 (95% CI: 1.23–7.04)	**FDG-PET and AVLT**
Chen et al. (2011)	Converters= 21 Non converters= 76	77.5 ± 6.9 74.9 ± 7.5	26.7±1.7 27.2±1.8	18	**FDG-PET**; Metric: HCI [33] HR= 7.38 (95% CI: 2.48–21.98)	**FDG-PET and sMRI**
Prestia al. (2015)	Converters= 29 Non converters= 44	67.6 ± 8.9 65.3 ± 9.4	26.7 ± 1.6 27.5 ± 1.8	23.6 ± 16.3	**FDG-PET**; Metric: PALZ [53] HR= 7.19 (95% CI: 2.76– 18.74)	**CSF Aβ42 and (FDG-PET or CSF tau)**
Shaffer et al. (2013)	Converters= 43 Non converters= 54	75.4 ± 7.2 74.7± 7.2	26.6 ± 1.7 27.5 ±1.6	20.7 ± 9.8	**FDG-PET**; Metric: ICA [36] AUC = 0.87*	**FDG-PET, sMRI, CSF tau, and CSF Aβ42** *
Schmand et al. (2012)	Converters= 81 Non converters= 94	74.4 ± 7.4 74.1 ± 7.6	26.6 ± 1.8 27.2 ± 1.7	32.4 ± 10.8	**sMRI**; Metric: ROI approach [39] AUC= 0.71 (0.64–0.77)	**sMRI, CSF Aβ42 and AVLT**
Yu et al. (2012)	Converters= 25 Non converters= 38	74 ± 5.6 74.8 ± 7.2	26.6 ± 1.87 27.3 ± 1.5	24	**sMRI**; Metric: ROI approach [37] Accuracy = 78 %	**sMRI, FDG-PET, CSF tau, CSF Aβ42, ApoE and ADAS-Cog**
Trzepacz et al (2014)	Converters= 20 Non converters= 30	75.4 ± 6.6 74.2 ± 8.4	26.2 ± 2.1 28.3 ± 1.6	24	**sMRI**; Metric: ROI approach [38] Accuracy = 71 %	**sMRI and amyloid PET (PIB)**

FDG-PET,fluorodeoxyglucose positron emission tomography; sMRI, structural magnetic resonance imaging; MMSE, Mini-Mental State Examination; AVLT; Auditory Verbal Learning Test; CSF, cerebrospinal fluid; ROI, region of interest; HR, hazard ratio; AUC, area under curve (receiver operating characteristic analysis); HCI, hypometabolic convergence index; PALZ, Alzheimer discrimination analysis tool; ICA; independent component analysis; ADAS-Cog, AD assessment scale-cognitive subscale score. * The value shown is FDG-PET in combination with covariates (age, education, ApoE genotype, and ADAS-Cog).

Landau et al. [33] studied various predictors in MCI subjects from the ADNI cohort. Predictors included metabolic measures by FDG-PET, hippocampal atrophy by sMRI, classical AD CSF protein biomarkers, APOE genotype and Auditory Verbal Learning Test (AVLT) as a measure of episodic memory. The metric used to assess AD-like hypometabolic pattern was the metaROI score [55]; while Freesurfer software was used to measure hippocampal volume [76]. Results showed that both metabolic measure and hippocampal atrophy using a univariate model were predictive of conversion. However, metabolic measure was the only predictive one in multivariate analysis. One of the main findings and conclusions was that FDG-PET combined with episodic memory score predicts conversion better than other predictor combinations (Table 1). This finding might be confounded by the diagnostic criteria of amnestic MCI, which already include impaired episodic memory. Another limitation is that no subgroup differences between non-anamnestic, single domain and multi-domain MCI could be reported, which may influence the diagnostic performance of imaging tools.

Chen et al. [35] introduced a new FDG-PET metric for AD assessment: the hypometabolic convergence index (HCI). They studied the capability of this metric in MCI subjects from the ADNI cohort. They also compared HCI score with hippocampal volume by sMRI, CSF biomarkers, memory test scores, and clinical ratings. They used a semiautomated method to measure hippocampal volume [69]. Similar to Landau et al. [34], they found that both metabolic measure (HCI score) and hippocampal atrophy were predictive of conversion by univariate model, although slightly better for HCI score (Table 1), but both exceeded CSF biomarkers, memory test scores and clinical ratings. They also found that HCI score and hippocampal atrophy were the only ones that predicted conversion using a multivariate model. Moreover, a combination of high HCI score and hippocampal atrophy predicted conversion from MCI to AD significantly better than each predictor separately. Although these results

overlap with the results of Landau et al. [34] regarding the predictive power of the FDG-PET, they also differ in that the memory test scores in the multivariate model were not predictive, even though AVLT was used among the memory test scores.

Similar to the two studies previously discussed, Prestia et al. [36] compared FDG-PET, hippocampal volume by sMRI and CSF proteins, to predict progression from MCI to AD. However, some specific aspects set this study apart. First, the study was conducted in two independent cohorts, ADNI (mean follow up period of 26 months; 24 converters and 28 non-converters) and the Translational Memory Outpatient Clinic (TOMC cohort; mean follow up period of 36 months; 18 converters and 28 non converters) of the Scientific Institute for the Research and Care of AD, in Brescia, Italy. The second aspect is that they used three different metrics for FDG-PET assessment, and another three different metrics for hippocampal volume. In the case of FDG-PET, they used metaROI score [55], similar to Landau et al. [34]; HCI score, similar to Chen et al. [34]; and the Alzheimer discrimination analysis tool (PALZ) [56]. For hippocampal volume measurement, the authors used manual tracing (TOMC cohort); a semi-automated method [70] (TOMC and ADNI cohorts); and a fully automated method by Freesurfer software [76] (TOMC and ADNI cohorts). The final aspect is that multivariate analysis was not performed. They found that semiautomated hippocampal volume and HCI hypometabolic metrics gave similar results and had the highest accuracy to predict conversion, although hippocampal volume metric was slightly better; whereas in the TOMC cohort, it was the PALZ hypometabolic metric, though comparable to CSF tau and CSF Aβ42. It is noteworthy that in both cohorts the three hypometabolic metrics showed the best balance of sensitivity and specificity compared with other biomarkers. Also interestingly, compared with the ADNI cohort the accuracy to predict conversion was higher in the TOMC cohort for all biomarkers, excluding hippocampal volume. The authors noted that this would be clarified in further studies, but hypothesized that this might be related to differences

between cohorts with regard to cognitive reserve and APOE genotype. They also showed that in both cohorts an abnormal measure of CSF Aβ42 was the most sensitive biomarker, which is in agreement with the biomarker model [1-6]. At the same time, they found that CSF Aβ42 alone showed the lowest specificity, thus confirming the need for combining amyloidosis and neuronal injury biomarkers to improve identification of subjects with MCI due to AD. Moreover, while they found that FDG-PET (PALZ metric) was a superior method to predict conversion in the TOMC cohort, they concluded that CSF Aβ42 in combination with hippocampal volume could be the best option to identify MCI subjects at risk of developing AD, mainly in terms of cost and benefits for clinical trial design. Galluzzi et al. [78] reached similar conclusions using only MCI subjects from the TOMC cohort (small sample) and the same analysis methods used by Prestia et al. in this dataset. The importance of this study is that it was able to demonstrate the validity of the biomarkers model in two samples of different datasets. A limitation is that multivariate analysis was not performed, unlike studies of Landau et al. [34] and Chen et al. [35]. Thus, it was not possible to study different combinations of biomarkers properly.

In a more recent article, Prestia et al. [37] performed a more elaborate second study on the same topic, this time using multivariate analysis. In the latter study, MCI subjects from three European memory clinics were evaluated, including TOMC cohort and two others cohorts, one from Amsterdam, The Netherlands, and another from Stockholm, Sweden. The authors compared the accuracy of various biomarkers for AD prediction individually and in combination. Biomarkers included FDG-PET (PALZ metric) and hippocampal atrophy (sMRI-based automated method) and classical CSF protein biomarkers. It is important to note that this study for the first time compared two sets of biomarker based diagnostic criteria of the prodromal AD stage, the NIA-AA criteria [14] and the International Working Group (IWG) criteria proposed by Dubois et al. [79, 80], respectively. The main findings were that

the highest accuracy for AD prediction was achieved by combining amyloidosis and neuronal injury biomarkers; whereas FDG-PET was the best predictive biomarker individually (Table 1), concurrent with the results of Landau et al. [34] and Chen et al. [35]. They also found that the IWG criteria have higher sensitivity but lower specificity than the NIA-AA criteria.

Shaffer et al. [38] used ICA to extract independent sources of information from the whole brain, for both FDG-PET and sMRI in MCI subjects from the ADNI dataset. By using logistic regression, the loading parameters for all FDG-PET and sMRI components and CSF proteins were modeled as independent variables, while conversion to AD within 4 years was the dependent variable. They studied several combinations of FDG-PET, sMRI, and CFS biomarkers with clinical covariates, including age, education, APOE genotype and the AD assessment scale-cognitive subscale (ADAS-Cog). Main results showed that the combination of all biomarkers with clinical covariates significantly increased the predictive power compared with clinical covariates alone. Nevertheless, they found that FDG PET was the main contributor (Table 1), in agreement with the studies discussed above. This study showed that similar results are reached using non-conventional methods such as ICA.

On the other hand, in the last five years, several studies have suggested that sMRI provides more prognostic information compared with FDG-PET. Using a Bayesian classification approach Yu et al. [39] compared FDG-PET, sMRI, CSF proteins, APOE genotype, and the ADAS-Cog score to predict conversion from MCI to AD within 2 years follow up. FDG-PET and sMRI were analyzed using methods based on regions of interest (ROI), including metaROI [55], HCI metrics [35], and UCSD software for sMRI [71]. They found that sMRI had the highest predictive accuracy (Table 1), followed by APOE genotype, FDG-PET, CSF proteins, and ADAS-Cog score. They also found that the combination of different biomarkers improved accuracy for AD prediction. They concluded that the combination of sMRI, APOE genotype, and cognitive measures provided the optimal trade-off between cost and time

compared with other combinations of biomarkers for enriching MCI samples for clinical trials. While these findings are interesting, one of the limitations of this study was that in order to measure the predictive power of each biomarker separately, the authors used much smaller MCI subject samples for CSF proteins and FDG-PET evaluation.

Trzepacz et al. [40], using multivariate models, compared FDG-PET, sMRI, amyloid PET using Pittsburgh compound-B (PIB), APOE genotype, age and education to predict AD conversion in MCI subjects (ADNI cohort). They did not include cognitive measures in their analyses. All imaging modalities were analyzed using ROI approaches, similar to the work by Yu et al. [39]. The authors found that sMRI combined with PIB-PET showed the highest predictive accuracy; whereas individually sMRI was the best predictive biomarker (Table 1) in comparison with FDG-PET and PIB-PET. APOE genotype, age and education did not show predictive value. The authors also found that PIB-PET had the highest sensitivity, while FDG-PET had the lowest. However, FDG-PET had the highest specificity compared with each imaging modality separately or any combination of these modalities. The importance of this study is that it shows the usefulness of amyloid PET in combination with neuronal injury biomarkers for predicting conversion in MCI subjects.

Schmand et al. [41] investigated the value of FDG-PET, sMRI, CSF protein biomarkers and cognitive measures to predict conversion to AD in MCI subjects using logistic regression models (ADNI cohort). One interesting aspect of this study is that the authors, based on previous findings [42], examined the effect of age on the predictive value of these methods by dividing the whole MCI sample into two subsamples, with ages below 75 years (relatively young subsample) and higher than 75 years (old subsample). The metrics used for FDG-PET and sMRI were based on ROIs approach (including hippocampal volume for sMRI) [41]. They found that in the whole MCI sample all methods were predictive, but sMRI scored best (Table 1), followed by cognitive measures, CSF Aβ42 and FDG-PET. In the relatively young

subsample, sMRI and cognitive measures had the same predictive value, followed by CSF Aβ42 and FDGPET; while in the old subsample sMRI was the best, followed by cognitive measures and CSF Aβ42. In this subsample FDG-PET had no significant predictive value. An interesting result was that the model combining all methods was not predictive in the old subsample. However, the model was so after excluding FDG-PET. They concluded that in MCI subjects older than 75 years, FDG-PET and CSF biomarkers are less informative, unlike sMRI and cognitive measures that remain useful.

Perhaps one of the most revealing studies published in recent years is that of Dukart et al. [43]. This study might explain the discrepancies observed in several previous studies regarding the predictive value of FDG-PET and sMRI. The authors realized that the majority of previous studies did not take into account the effects of age, except for instance the studies by Schmand et al. [41, 42], symptom severity or time to conversion from MCI to AD. They compared FDGPET and sMRI by selecting samples of similar size of nonconverters MCI (N= 65) and converter MCI subjects (N= 64) from the ADNI cohort. They also included a sample of 80 AD patients. The three patient groups were then divided into subgroups by age and disease severity. Thus, for example, they constituted nine subgroups according to age: three subgroups of non-converters MCI (ncMCI) subjects, one consisting of young subjects, one of middle age subjects, and another one of old age subjects (mean age of 68.0, 75.7 and 82.6 years of each subgroup, respectively). In the same way, they formed three subgroups of converter MCI (cMCI) (mean age of 67.9, 75.6 and 82.0 years) subjects and three subgroups for AD patients (mean age of 69.2, 75.6 and 82.2 years, Fig. 3). Fig. (3) shows that in the young cMCI subgroup hypometabolism predominated largely over atrophy and was more extensive (easier to detect) compared with middle and old age cMCI subgroups; whereas hypometabolism and atrophy were more or less similar in other cMCI subgroups. In contrast, atrophy predominated largely over hypometabolism in the three AD patient subgroups. The

authors also used a similar procedure to constitute nine cMCI subgroups according to disease severity using the Mini- Mental State Examination (MMSE) (Fig. 4). As can be observed in this Figure, hypometabolism predominated over atrophy in cMCI subgroups with less severity (mean MMSE of 28.8 and 26.9, respectively), while atrophy was more extensive in the cMCI subgroup with more severity (mean MMSE= 24.8) compared with other cMCI subgroups. Similar to the age effect, atrophy prevailed over hypometabolism in the three AD patient subgroups. Figs. (3 and 4) show other results that allow better appreciation what happens to brain metabolism and volume in different situations according to age and severity of clinical symptoms. To evaluate the effect of conversion time, the authors divided the whole cMCI group into three subgroups. Fig. (5) shows that hypometabolism predominated over atrophy in the cMCI subgroups converting in 12 and 18 months, whereas hypometabolism and atrophy were comparable in the cMCI subgroup converting in 24 months. The authors concluded that FDG-PET might be a more sensitive biomarker of disease progression at the MCI stage, whereas sMRI appears to be more linked to the existing global cognitive state, possibly reflecting permanent injury. This is consistent with the notion that the reduced consumption of glucose at the synaptic level precedes neuronal loss.

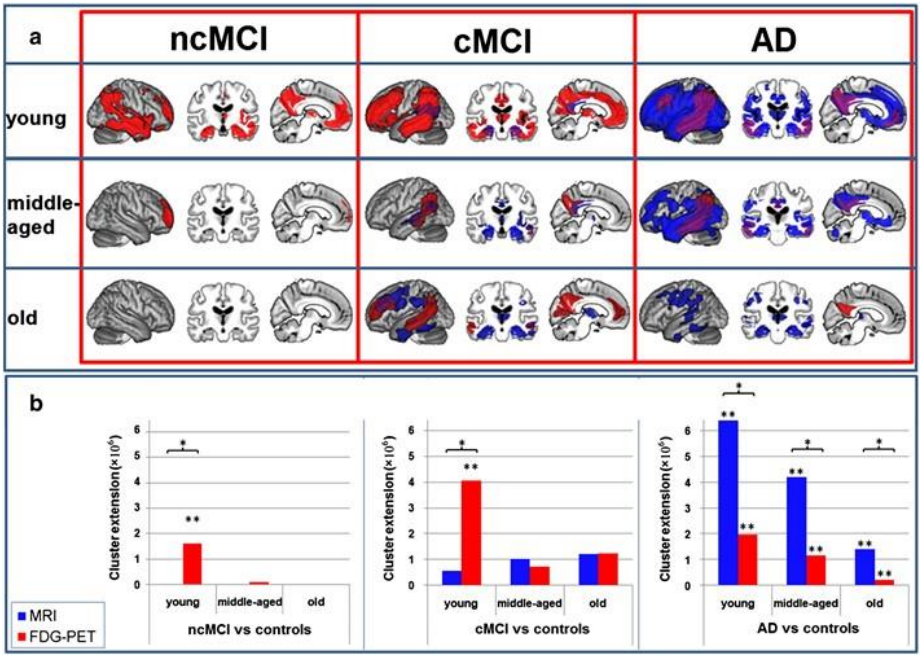

Fig. (3). MRI and FDG-PET results for the comparison of three groups of AD patients, MCI converters (cMCI) and non-converters (ncMCI) split by age compared to the same group of control subjects. a) MRI (blue: hippocampal atrophy) and FDG-PET (red: hypometabolism) results plotted onto an averaged brain. Overlapping results are displayed in violet. Results for differently aged subgroups are separated by rows. Results for different clinical groups are separated by columns. Cortical hypometabolism in ncMCI patients was restricted to the right hemisphere. In contrast, in both other groups the results were much more symmetric however with more extensive changes in the left hemisphere. b) Number of significant voxels (p = 0.001 uncorrected at voxel level and p = 0.05 FWE corrected at cluster level) detected in each comparison in FDG-PET (red) and MRI (blue). AD Alzheimer's disease, FDG-PET [18F] fluorodeoxyglucose positron emission tomography, FEW family-wise error, MCI Mild Cognitive Impairment, MRI structural magnetic resonance imaging, * indicates a significant difference between modalities within the condition, ** indicates a significant difference to all other conditions within the modality. (For interpretation of the references to colour in this

Figure legend, the reader is referred to the web version of this article.). From J. Dukart et al. NeuroImage: Clinical 3:84-94 (2013).

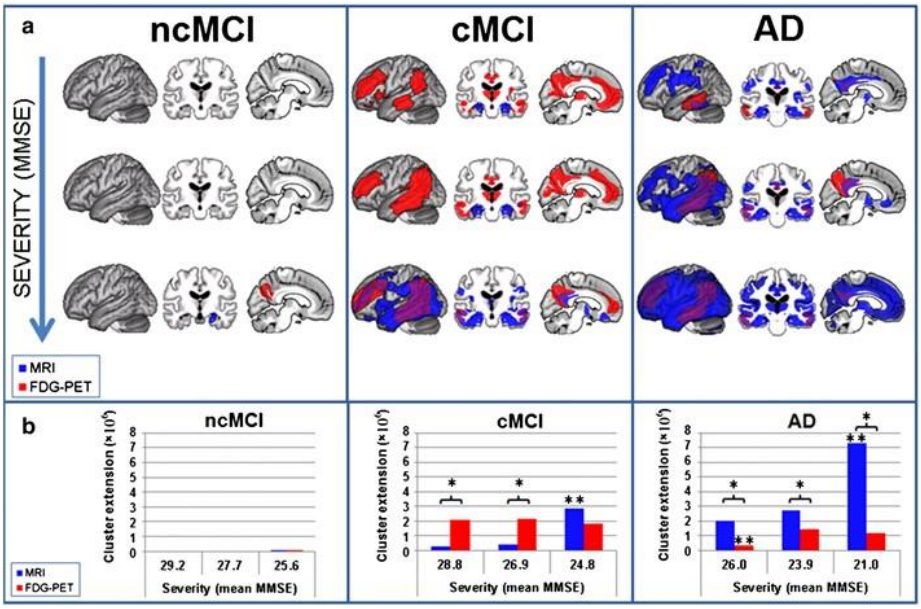

Fig. (4). MRI and FDG-PET results for the comparison of three groups of AD patients, MCI converters (cMCI) and non-converters (ncMCI) split by symptom severity compared to the same group of control subjects. a) MRI (blue: hippocampal atrophy) and FDG-PET (red: hypometabolism) results plotted onto an averaged brain. Overlapping results are displayed in violet. Results for differently affected subgroups are separated by rows. Results for different clinical groups are separated by columns. b) Number of significant voxels (p = 0.001 uncorrected at voxel level and p = 0.05 FWE corrected at cluster level) detected in each comparison in FDG-PET (red) and MRI (blue). AD Alzheimer's disease, FDG-PET [18F]fluorodeoxyglucose positron emission tomography, FWE family-wise error, MCI Mild Cognitive Impairment, MRI structural magnetic resonance imaging, * indicates a significant difference between modalities within the condition, ** indicates a significant difference to all other conditions within the modality. (For interpretation of the references to colour in this Figure legend, the reader is referred to the web version of this article.). From J. Dukart et al. NeuroImage: Clinical 3: 84-94(2013).

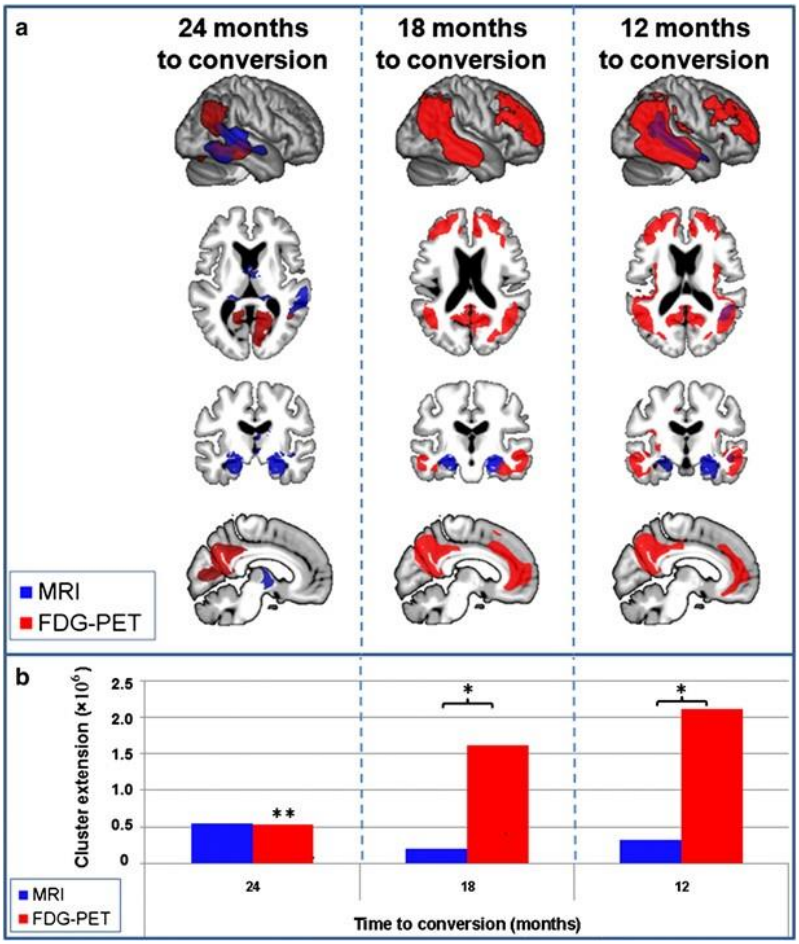

Fig. (5). MRI and FDG-PET results for the comparison of three subgroups of MCI converters split by time to conversion compared to the same group of control subjects. a) MRI (blue: atrophy) and FDG-PET (red: hypometabolism) results plotted onto an averaged brain. Overlapping results are displayed in violet. Results for different subgroups are separated by columns. b) Number of significant voxels (p = 0.001 uncorrected at voxel level and p = 0.05 FWE corrected at cluster level) detected in each comparison in FDG-PET (red) and MRI (blue).AD Alzheimer's disease, FDG-PET [18F]fluorodeoxyglucose positron emission tomography, FWE family-wise error, MCI Mild Cognitive Impairment, MRI structural magnetic resonance imaging, * indicates a significant difference between modalities within

the condition, ** indicates a significant difference to all other conditions within the modality. (For interpretation of the references to colour in this Figure legend, the reader is referred to the web version of this article.). From J. Dukart et al. NeuroImage: Clinical 3: 84-94 (2013).

In addition, the temporal distribution of alterations during conversion may be dependent on specific regions of the brain. La Joie and colleagues applied voxel based methods to compare results of FDG imaging, sMRI and amyloid imaging (18F-florbepatir) in 22 patients with a high probability of AD [44]. They reported high correlations between areas of hypometabolism and atrophy in large parietotemporal areas, although substantial regional variability in both directions was present. Atrophy exceeded hypometabolism in the hippocampal-amygdala complex, whereas hypometabolism was more excessive in prefrontal regions. On the other hand, no significant correlation between Aβ deposition and hypometabolism and atrophy was found and particularly high Aβ depositions were observed in frontal regions. The results are supportive of the concept that the effect of Aβ depositions may not be local, but rather distant.

Another revealing study is the meta-analysis recently published by Frisoni et al. [45]. This study illustrates that the predictive power of imaging biomarkers heavily relies on how they are measured. The authors evaluated the diagnostic accuracy of different imaging biomarkers versus metrics in separating AD from healthy subjects, and prognostic accuracy to predict progression in MCI individuals. The metaanalysis included various studies that used different imaging biomarkers (PET amyloid, FDG-PET, perfusion SPECT and sMRI) and the most commonly metrics used. They used positive (LR +) and negative (LR-) likelihood ratios as outcome measures to examine the variability due to metrics and imaging biomarkers (or submarkers, e.g. specific brain region for sMRI). They considered LR + > 5 and LR- ≤ 0.2 as diagnostically useful. They found that diagnostic accuracy was highest for PET amyloid,

followed by FDG-PET, perfusion SPECT and sMRI. On the other hand, the prognostic accuracy to predict progression was highest for FDG-PET followed by sMRI, perfusion SPECT and PET amyloid. The LR analysis for prognosis showed that FDG-PET was the only one with LR+ greater than 5, followed by sMRI (LR+=2.6), perfusion SPECT (LR+= 2.2) and PET amyloid (LR+=1.7). sMRI submarkers showed LR+ of 2.2 for entorhinal cortex and 2.9 for hippocampus. They also found that PET amyloid showed the best LR- (0.11), followed by sMRI (0.49) and FDG-PET (0.5). The variability of metrics for FDG-PET was the highest. They concluded that diagnostic and prognostic accuracy of imaging biomarkers is at least as dependent on how the biomarker is measured as on the biomarker itself.

There have been other studies using data from the ADNI cohort that suggest that cognitive measures may be equal or more predictive than FDG-PET, sMRI and CSF proteins [81-84]. However, these findings cannot be generalized to MCI subjects outside ADNI dataset, which is a highly selected convenience sample.

In the last five years there are also studies suggesting that the combination of baseline and longitudinal data of both FDG-PET and sMRI significantly improves the prediction of AD dementia in MCI subjects compared to baseline data alone or each data separately [85-88]. Although repetitive scanning may be impractical in clinical routine, these findings could be relevant for recruitment of subjects into clinical trials, in which a greater certainty is required as to whether a candidate meets the selection criteria. Clinical trials of potential disease-modifying therapies for AD in MCI patients benefit from the enrichment of the study samples with MCI due to AD cases.

There are other recent studies that have developed new methodologies to improve prediction accuracy based on machine learning tools combining information from FDG-PET, sMRI and other biomarkers [83, 89-95]. These methodologies have shown great potential to perform computer assisted classification of MCI converters and MCI non-converters.

As a final point, a recent study has shown that FDG-PET predicts decline in cognitive functions among cognitively normal subjects [96]. This has important implications since research efforts move toward early identification of high risk individuals and prevention of clinical progression. Thus, FDG-PET might play a role as an early biomarker of neuronal injury even in preclinical stages of AD [97].

In summary, recent literature shows that FDG-PET and sMRI are useful for prediction of AD dementia in MCI. However, there are conflicting results as to which neuronal injury imaging biomarker is superior (Table 1). This could be explained by the high variability of metrics used to evaluate both imaging modalities. Moreover, the majority of published studies did not take into account various factors that could influence the results, such as age, symptom severity and conversion time. However, FDG-PET seems to perform better in rapidly converting relatively young MCI subjects, whereas sMRI may be superior in older MCI individuals. In the latter situation, FDG-PET imaging might be redundant, although additional regions of impairment may be detected, in which case it would provide complementary role. The recent literature confirms that the highest accuracy for AD prediction is achieved by combining amyloidosis and neuronal injury biomarkers, more specifically FDG-PET or sMRI, which is in line with the biomarkers model [6] and the recent criteria of MCI due to AD proposed by the NIA-AA [16]. Perhaps one of the main problems to fully generalize these recent findings is that they are based on ADNI subjects, which have been uniquely selected and might not represent community subjects with MCI.

3. PERFUSION SPECT AS ALTERNATIVE TO FDG-PET

Perfusion SPECT is an indicator of regional cerebral blood flow (CBF) which is tightly coupled with regional brain glucose metabolism in many neurologic diseases, such as AD. The most widely used radiopharmaceuticals for perfusion SPECT are 99mTc-labelled compounds, hexamethylpropylene amine oxime (HMPAO) and ethyl cysteine dimer. In

Japan, 123I-N-isopropyl-p-iodoamphetamine is used also. Major advantages of perfusion SPECT are that it is available worldwide and much cheaper (approximately 2 -3 times less) in comparison to FDG-PET. The major disadvantage is its lower spatial resolution (≈ 8-10 mm) versus FDG-PET (≈ 4-5mm).

The AD-like pattern detected by FDG-PET is also observed using perfusion SPECT (Fig. 6). Herholz et al. [98] found that the number of abnormal voxels for FDG-PET correlated strongly (r= 0.90) with the number for perfusion SPECT (HMPAO) in the temporoparietal cortices (the AD-like pattern), although it was less pronounced using perfusion SPECT than FDG-PET. Likewise, visual reading may be improved by the use of quantitative metrics, especially in MCI patients. In principle, the same metrics used for FDG-PET to detect the AD-like pattern can be used for perfusion SPECT. Probably the positive impact of the use of quantitative metrics is greater for perfusion SPECT than for FDG-PET.

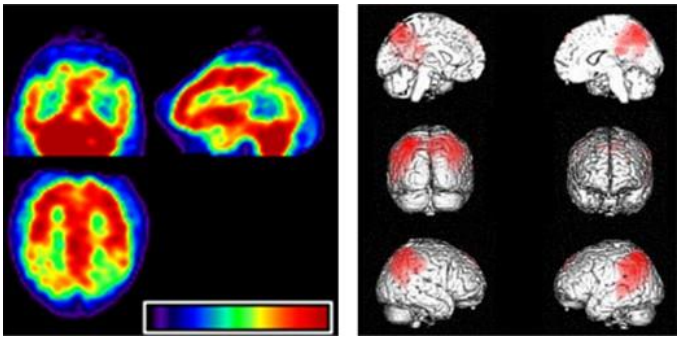

Fig. (6). The AD-like pattern by perfusion SPECT (99mTc-ECD). Left side shows coronal, sagittal and axial selected slices illustrating the AD-like pattern of temporoparietal hypoperfusion in a 70-year-old male patient with probable AD dementia (MMSE= 21) according to the NIA-AA criteria. Right side shows the SPM-t map for this patient in comparison to the normal control database. The patient was examined in the Center for Neurological Restoration, Havana, Cuba.

At the beginning of this century, a landmark study of Jagust et al. [97] clearly showed that perfusion SPECT improves clinical diagnosis of AD, especially in the earliest stage. The importance of this study is that it was based on comparing perfusion SPECT and ante-mortem clinical diagnosis of AD, individually and combined, with post-mortem findings in patients and control individuals. The post-mortem analysis is considered the gold standard for AD diagnosis.

Table 2. Pooled sensitivity and specificity of perfusion SPECT and FDG-PET for prognosis and diagnosis of Alzheimer's disease, based on recent meta-analyses.

Meta-analysis	**Perfusion SPECT for prognosis**		**FDG-PET for prognosis**	
	Pooled Sensitivity	Pooled Specificity	Pooled Sensitivity	Pooled Specificity.
Yuan et al. (2009) [25]	84%	70%	89%	85%.
	172 converters MCI (8 studies)		134 converters MCI (6 studies)	
Frisoni et al. (2013) [42]	78 %	64 %	76 %	74%.
	166 progressed MCI (6 studies)		241progressed MCI (10 studies)	
	Perfusion SPECT for diagnosis		**FDG-PET for diagnosis**	
Frisoni et al. (2013) [42]	76%	84%	86%	84%
	1268 AD patients (32 studies)		1897 AD patients (37 studies)	
Bloudek et al. (2011) [106]	80%	85%	90%	89%
	Not available (11 studies)		Not available (20 studies)	

Like FDG-PET, perfusion SPECT has been effectively used to predict AD dementia in MCI subjects [98-111] and it has been also the subject of recent reviews [26, 45, 114-118]. Three meta-analyses and one systematic review have been published [26, 45, 117, 118], two recent [45, 118], which are revealing with regard to the comparison of perfusion SPECT with FDG-PET.

The first of these meta-analyses is the aforementioned of Yuan et al. [26]. They found that FDG-PET performs slightly better than perfusion SPECT for predicting conversion to AD

dementia (Table 2). It may be noted that the superiority of FDG-PET was mainly in its specificity. They also found similar performances for perfusion SPECT and sMRI.

The second meta-analysis is by Frisoni et al. [45], already partially discussed before. As explained one of the objectives of this study was to evaluate the prognostic accuracy of different imaging biomarker versus the metrics to predict progression in MCI individuals. They found that pooled sensitivity and specificity, across all metrics, were lower than those reported by Yuan et al. [26], for both perfusion SPECT and FDG-PET (Table 2), probably because metrics showed high variability in both cases [45]. However, it may be noted that in both meta-analyses, the superiority of FDG-PET was limited, at its best for specificity. Frisoni et al. [45] also analyzed the diagnostic accuracy for separating AD patients from controls. As can be seen in Table 2, the diagnostic performance was better than the prognostic one for both imaging modalities, especially the specificity for perfusion SPECT which was similar to that of FDG-PET for diagnostics.

The third meta-analysis was conducted by Bloudek et al. [117]. They analyzed articles for diagnostic imaging in AD, including perfusion SPECT and FDG-PET. They found that pooled sensitivity and specificity were comparable to those reported by Frisoni et al. [45] (Table 2).

The fourth study reviewed all published head-to-head studies comparing perfusion SPECT and FDG-PET in AD and other dementias [118]. Although the reviewed studies had several limitations, especially small sample sizes, the results showed that most of studies found perfusion SPECT to be useful and often as good as FDG-PET to detect temporoparietal changes (the AD-like pattern). In four subsequent studies to the meta-analysis of Yuan et al. [26] (two using perfusion SPECT and two by FDG-PET), the authors also evaluated the pooled prognostic accuracy. They found similar sensitivity for both imaging modalities, but higher specificity for perfusion SPECT. They concluded that although studies suggest

superiority of FDG- PET over perfusion SPECT, the evidence for this is limited. They suggested further direct comparative studies, including health economic and patient preference evaluations. Although the superiority of FDG-PET in AD is unquestionable, especially because of its better spatial resolution, data published to date do not support the exclusion of perfusion SPECT as a valid alternative when FDG-PET is not available, whatever the reason. In fact, as noted in the introduction in 2011 the NIA-AA criteria of MCI due to AD, recognized perfusion SPECT as an equivalent biomarker to FDG-PET [15].

Lastly, while the quality of the instrumentation and the use of rigorously validated standards for image acquisition, pre/post processing and metrics to evaluate the images of both imaging modalities is important, it is even more crucial for perfusion SPECT as it is more subject to noise (less counts are acquired). Therefore, special attention should be paid to these technical and methodological aspects when perfusion SPECT is used, especially as predictive biomarker in prodromal AD.

4. FUTURE DIRECTIONS

As discussed in the above, conflicting results concerning the respective predictive values of FDG-PET and sMRI exist, which to some extent can be explained by the high variability of metrics used to evaluate both imaging biomarkers. This highlights the importance of standardized metrics and the need for the development of standard operating procedures for clinical and research use. Moreover, although FDG-PET might be superior in some clinical situations and sMRI in others, more studies are necessary to confirm their respective roles by using longitudinal data from larger cohorts of converted MCI subjects, preferably with postmortem verification. To this end, a multicenter study, preferentially consisting of a community based dataset, would be the most desirable option. In this perspective, novel MRI-PET hybrid implementations could facilitate data acquisition and diminish the burden to the patient. Further studies are also needed to address the cost and benefits of FDG-PET

compared with sMRI or other neuronal injury biomarkers for both research and clinical settings.

One of the new directions of AD research in recent years has been the search for abnormalities that might precede amyloidosis, which could have implications for the development of AD biomarkers at early disease stages. One example of this is the study of the default mode network (DMN). The DMN is particularly relevant for aging and AD since DMN structures are vulnerable to Aβ deposition, hypometabolism and atrophy [119, 120]. DMN abnormalities have been observed along a continuum from normal aging to AD dementia by using different neuroimaging modalities and analysis methodologies (reviewed in [121]). Graph theoretical analysis is an emerging analysis methodology that has been effectively used to study properties of brain functional networks (reviewed in [122]). Recent studies have shown that graph theoretical analysis of FDG-PET data is a promising pathway that could help to better understand the characteristics of brain functional networks, in normal aging, MCI, and AD dementia [123-125].

On the other hand, there is increasing evidence supporting that subtle dysfunction of small vessels in the brain might play a role at beginning of AD pathology [126, 127]. This could also have implications for the development of biomarkers for the very early stages of AD. Using graph theoretical analysis, a recent study demonstrated that the CBF-related network, constructed from perfusion SPECT data in healthy controls, shows a small-world architecture [128], similar to other brain networks. This study constitutes a first step to explore changes in the topology of the CBF network in neurological diseases with possible involvement of small vessels such as AD.

Another research direction is the combination of FDG-PET and /or perfusion SPECT with arterial spin labeling MRI (ASL-MRI). ASL-MRI is a completely non-invasive technique to quantify CBF. Recently, patterns of hypoperfusion similar to perfusion SPECT were observed

in patients with clinically suspected AD by using ASL-MRI [129]. In another study, ASL-MRI was comparable to FDG-PET in differentiating a group of patients with dementia AD and FTD [130]. Chen et al. also found largely identical regions of reduced functionality in patients with AD compared to age-matched controls [131]. In subjects with MCI, regional perfusion deficits detected using ASL-MRI in the right middle parietal and right middle frontal regions have been associated with conversion to dementia during follow-up [132]. Analogous to FDG-PET and perfusion SPECT, ASL-MRI has been suggested to have predictive value in the preclinical stage of AD [133]. Using ASL, hypoperfusion in the posterior cingulae cortex at baseline has been found in healthy elderly patients at baseline who develop subsequent cognitive deterioration [134]. Thus ASL-MRI has the potential to serve as a biomarker in the early diagnosis of preclinical dementia. Since structural MR imaging is routinely performed in many centers during the work-up of cognitive decline, ASL might simply be added to an existing investigation. Another advantage of combining functional imaging with structural MRI, is the identification of vascular aberration (i.e. calfications, infarctions, white matter lesions and microbleeds). Although ASL-MRI is a promising tool, further research is necessary to establish its role in the management of dementias, especially in the preclinical stages of AD.

A multimodal framework combining molecular imaging such as FDG-PET and amyloid PET, with advanced MRI techniques such as ASL, resting-state functional connectivity, susceptibility imaging, diffusion tensor imaging and/or MR spectroscopy could be of value in the detection of functional impairments which may precede amyloidosis in AD.

CONCLUSION

Recent studies confirm previous findings concerning the effectiveness of FDG-PET as a biomarker of neuronal injury, with predictive value towards the conversion to AD dementia in MCI subjects. FDG-PET seems to outperform to sMRI in rapidly converting early-onset MCI

individuals, whereas sMRI may outperform FDG-PET in late-onset MCI subjects, in which case FDG PET might only provide a complementary role. Further studies are required to support this conceptualization. In addition, recent findings show that the highest diagnostic accuracy to predict conversion of MCI to AD is achieved using a combination of cerebral amyloid burden and neuronal injury biomarkers, consisting of FDG-PET or sMRI. On the other hand, despite the common notion that FDG-PET performs better than perfusion SPECT, current evidence and guidelines support the clinical utilization of perfusion SPECT as a valid - less costly and more accessible- alternative to FDG PET. Finally, further cost-effectiveness analyses are necessary to compare FDG-PET and perfusion SPECT with structural and advanced MRI and other neuronal injury biomarkers for both clinical and research use. Multi-modal imaging techniques such as PET-MRI are expected to improve the early diagnosis of AD and differentiate between AD and other forms of dementia.

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